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(54) Title: COMBINATION OF TEMOZOLOMIDE AND ALPHA-IFN FOR THE TREATMENT OF ADVANCED CANCER

(57) Abstract

There is disclosed a method for treating advanced cancer in patients in need of such treating. Temozolomide and alpha interferon are administered in combination in amounts sufficient to achieve a clinical response.

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COMBINATION OF TEMOZOLOMIDE AND ALPHA-IFN FOR THE TREATMENT OF ADVANCED CANCER

Despite the numerous advances in cancer treatment, the well-known life style changes that can greatly reduce the risk of cancer, and the early warning signs that some cancers provide, many patients still develop advanced cancer for which no conventional therapies are available that offer any reasonable hope of cure or significant palliation. This invention is the use of two known anti-tumor agents in combination therapy to provide a positive effect on such advanced cancers. It is also expected that the combination therapy will allow the administration of the two anti-tumor agents in quantities that will not result in intolerable side effects.

Temozolomide is known for its anti-tumor effects. For example, in one study clinical responses were achieved in 17% of patients having advanced melanoma (Newlands ES, et al. Br J Cancer 65 (2) 287-2981, 1992). In another sudy a clinical response was achieved in 21% of patients with advanced melanoma (Journal of Clinical Oncology, Vol 13, No. 4 (April), 1995, pp 910-913). However, temozolomide is not always effective and has dose-limiting side effects, such as hematologic toxicity, myelosuppression, anemia, leukopenia, etc.

Alpha interferon is also known to have anti-cancer effects. See, for example, Emstoff et al., Intravenous (IV) Recombinant α-2 Interferon in Metastatic Melanoma, Proc ASCO 2:57 (C-222), 1983. However this treatment is not always effective and sometimes results in intolerable side effects related to the dosage and duration of therapy.

There is a need for a method for treating advanced cancers with higher response rates or reduced side effects, or both.

SUMMARY OF THE INVENTION

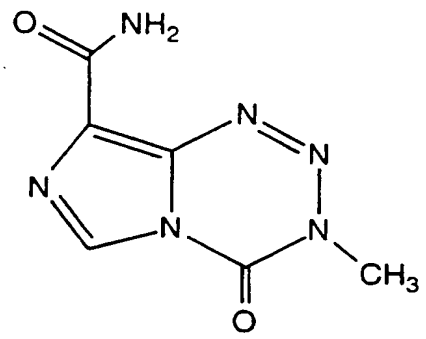
This invention may be summarized as a method for treating advanced cancer in patients in need of such treating comprising administering

temozolomide and alpha interferon in amounts sufficient to achieve a clinical response. The temozolomide is administered to the patient in combination with the alpha interferon, that is, the temozolomide and alpha interferon doses are administered during the same period of time. Preferred specific dosing schedules are given below.

DETAILED DESCRIPTION

All references cited herein are incorporated herein by reference.

The term "temozolomide" is intended to mean a compound having the formula.



One chemical name for temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo-[5,1-d]1,2,3,4-tetrazin-8-carboximide. The synthesis of temozolomide is well known. See, for example, Stevens et al., J. Med. Chem, 1984, 27, 196-201 and Wang et al., J. Chem. Soc., Chem. Commun., 1994, pp 1687-1688.

The term "alpha interferon" as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable alpha interferons include but are not limited to recombinant interferon alpha-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alpha-2a such as Roferon A interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofor alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alpha interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from th Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon available from Amgen, Inc., Newbury Park, CA, or

interferon alpha-n3 a mixture of natural alpha interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alpha-2a or alpha 2b is preferred. Interferon alpha 2b is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901. Of course the term alpha interferon includes the obvious equivalents thereto such as certain beta interferons known to have properties similar to alpha interferon.

Advanced cancers treatable by this invention include malignant melanoma, malignant metastasized melanoma, cancer of the lung, cancer of the breast, brain cancer, ovarian cancer, cancer of the head and/or neck, sarcoma, prostate cancer, and other cancers known to be at least partially responsive to alpha interferon or temozolomide treatment, that have advanced to a stage where conventional therapy is unlikely to provide a cure.

A person suffering from advanced cancer may exhibit one or more of the following signs or symptoms:

(a) presence of cancerous tumor,

(b) fatigue,

(c) pain,

(d) decreased performance status from tumor burden, and

(e) the well known symptoms associated with each specific cancer.

To practice the invention, temozolomide and alpha interferon are administered to the patient exhibiting one of more of the above signs or symptoms in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms.

The preferred dosage of temozolomide for practicing the combination therapy of this invention is 50 to 400 mg per m^2 of the patient's body surface area per day, more preferably 75 to 300 mg/m^2 and most preferably 100 to 200 mg/m^2/day. It is preferred that the daily dosage of temozolomide be administered once per day for a 2 to 10 day period, more preferably for a 3 to 8 day period and most preferably for a 5 day period. The temozolomide dosing periods may be repeated in cycles of 28 to 42 days, more perferably 28 to 35

days, and most preferably 28 days. That is, 28 to 42 days after the first day of temozolomide administration, another temozolomide administration period may be started.

Alternatively the temozolomide may be administered for a much longer period at reduced dosage. For example, the temozolomide could be administered daily for 11 days to six weeks at a dosage of 50 to 150 $mg/m^2/day$.

Temozolomide may be administered orally in capsule form wherein it is admixed with conventional pharmaceutical carriers. Preferred temozolomide capsule formulations are:

Ingredient	mg/Capsule			
temozolomide	5	20	100	250
Anhydrous Lactose NF	132.8	182.2	175.7	154.3
Sodium Starch Glycolate NF	7.5	11.0	15.0	22.5
Colloidal Silicon Diozide NF	0.2	0.2	0.3	0.7
Tartaric Acid NF	1.5	2.2	3.0	9.0
Steric Acid NF	3.0	4.4	6.0	13.5
Capsule Size*	3	2	1	0

* White opaque, preservative-free, two-piece hard gelatin capsules

It is especially preferred that the patient fast from all food or drink, except water, for four hours before temozolomide administration and for two hours after.

The alpha interferon is preferably administered by intrav nous or subcutantous injection beginning on day on of the first temozolomide administration period. However, unlike the temozolomide, the alpha interferon is administered more or less regularly throughout the combination therapy. The

alpha interferon may be administered 1 to 7 times per week, more preferably 2 to 5 times per week, and most preferably three times per week or every other day. The amount of alpha interferon per dose may be 1 million to 25 million international units (IU) per m^2 of patient's body surface area, more preferably 5 million to 15 million IU/m^2 and most preferably 7.5 million to 12.5 million IU/m^2.

The treatment may be continued until a clinical response is achieved or until intolerable side effects are encountered. The dosages of temozolomide and/or alpha interferon may be increased with each new treatment cycle, provided intolerable side effects are not encountered. The dosages may also be decreased, if intolerable side effects are encountered.

A common, but tolerable, side effect of temozolomide is nausea and vomiting. This can be alleviated by administering an anti-emetic in conjunction with the temozolomide. It is preferred that the anti-emetic Ondansetron be given p.o. in a dose of about 8 mg about 30 minutes before temozolomide administration. Of course other anti-emetics such as Haldol, Benadryl, and Ativan may also be used as needed.

A common, but usually tolerable, side effect of alpha interferon is flu-like symptoms. These can usually be alleviated with acetaminophen and other common aspirin-like medicines.

Of course, other forms of administration of both active ingredients, as they become available, are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, by IV injection, etc. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

The effectiveness of treatment may be determined by controlled clinical trials. Patients having advanced cancer with measurable or evaluable tumors will be included in the study. A measurable tumor is one that can be measured in at least two dimensions such as a lung tumor surrounded by aerated lung, a skin nodule, or a superficial lymph node. An evaluable tumor in one that can be measured in one dimension such as a lung tumor not compl tely surround d by aerated lung or a palpable abdominal or soft tissue mass that can be measured in one dimension. Tumor markers which have been shown to be highly correlated with extent of disease will also be considered to provide an

evaluable disease, such as PSA for prostate cancer, CA-125 for ovarian cancer, CA-15-3 for br ast cancer, etc.

The tumor will be measured or evaluated before and after treatment by whatever means provides the most accurate measurement, such as CT scan, MRI scan, Ultrasonography, etc. New tumors or the lack thereof in previously irradiated fields can also be used to assess the anti-tumor response. The criteria for evaluating response will be similar to that of the WHO Handbook of Reporting Results of Cancer Treatment, WHO Offset Publication 1979, 49-World Health Organization, Geneva. The following results are defined for uni- and bi-dimensionally measurable tumors.

Complete response: Complete disappearance of all clinically detectable malignant disease determined by two observations not less than four weeks apart.

Partial Response: (a) for bidimensionally measurable tumors, a decrease of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable tumors as determined by two observations not less than four weeks apart. (b) for unidimensionally measurable tumors, a decrease by at least 50% in the sum of the largest diameters of all tumors as determined by two observations not less than four weeks apart. In cases where the patient has multiple tumors, It is not necessary for all tumors to have regressed to achieve a partial response as defined herein, but no tumor should have progressed and no new tumor should appear.

Stable disease: (a) for bidimensionally measurable tumors, less than a 50% decrease to less than a 25% increase in the sum of the products of the largest perpendicular diameters of all measurable tumors. (b) for unidimensionally measurable tumors, less than a 50% decrease to less than a 25 % increase in the sum of the diameters of all tumors. For (a) and (b) no new tumors should appear.

No clinical response, i.e. progressive disease in defined as an increase of more than 50% in the product of the largest perpendicular diameters for at least one bidimensionally measurable tumor, or an increase of more than 25 % in measurable dimension of at least one unidimensionally measurable tumor.

For patients having both uni- and bi-dimensionally measurable tumors, the overall response will be determined in accordance with the following table.

Response in bidimensionally measurable disease	Response in unidimensionally measurable disease	Overall Response
PD	any	PD
Any	PD	PD
SD	SD or PR	SD
SD	CR	PR
PR	SD or PR or CR	PR
CR	SD or PR	PR
CR	CR	CR

Abbreviations: PD: Progressive Disease
CR: Complete Response
PR: Partial Response
SD: Stable Disease

Of course elimination or alleviation of other known signs or symptoms of advanced cancer, especially those listed previously can also be used to evaluate the effectiveness of this invention.

The advanced cancers should be evaluated, i.e. tumors measured, etc., no more than 14 days before the start of the treatment. These cancers should be reevaluated about 28 days after day 1 of administration of the first doses of temozolomide and alpha interferon. Twenty eight days after this initial administration another administration period may be performed, and evaluations performed 28 days after the start of this second cycle. The treatment cycles may be continued until a clinical response is achieved or unacceptable toxicity is encountered.

Another aspect of this invention is the treatment of advanced cancer with reduced side effects normally associated with temozolomide and alpha interferon. It is believed that this objective can be achieved by administration of lower doses of the two active ingredients or by shorter duration of dosing brought about by the synergistic effect of the combination.

The most serious side ffect of temozolomide is hematologic toxicity. Dos limiting toxicity for temozolomide is defined herein as

CTC Grade 4 neutropenia (absolute neutrophil count, including bands, of less than 0.5 X 10^3/ mm^3) which is not resolved in five days or

CTC Grade 4 anemia (hemoglobin of less than 6.5 g/dl), or

CTC Grade 3 thrombocytopenia (platelet count of less than 50 X $10^3/mm^3$) or

CTC Grade 4 thrombocytopenia(platelet count of less than 25 X $10^3/mm^3$).

The most common side effects of alpha interferon are:

- flu-like syndrone
- Neurotoxicity, including neuropsychiatric, neurosensory, and neuromotor,
- Cardiopulmonary
- Gastrointestinal, including nausea, vomiting, and/or diarreha
- Hepatotoxicity, including elevations of bilirubin, transaminases, or alkaline phosphatase
- Nephrotoxicity.

CLAIMS

1. A method for treating advanced cancer in patients in need of such treating comprising administering temozolomide and alpha interferon in amounts sufficient to achieve a clinical response.

2. The method of claim 1 wherein the amount of temozolomide administered is from 50 to 400 mg per m^2 of the patient's body surface area per day for a period of from 2 to 10 days and the amount of alpha interferon administered is from 1 million to 25 million IU per m^2 of the patient's body surface area administered intraveneously or subcutaneously 1 to 7 times per week.

3. The method of claim 2 wherein beginning 28 to 42 days after the first day of the temozolomide administration period, the temozolomide administrations are repeated.

4. The method of claim 3 wherein the alpha interferon administered is interferon alpha 2b.

5. The method of claim 2 wherein the amount of temozolomide administered is from 75 to 300 mg per m^2 of the patient's body surface area per day for a period of from 3 to 8 days and the amount of alpha interferon administered is from 5 million to 15 million IU per m^2 of the patient's body surface area administered intraveneously or subcutaneously.

6. The method of claim 5 wherein beginning about 28 to 35 days after the first day of the temozolomide administration period, the temozolomide administrations are repeated.

7. The method of claim 6 wherein the alpha interferon administered is interferon alpha 2b.

8. The method of claim 5 wherein the amount of temozolomide administered is from 100 to 200 mg per m^2 of the patient's body surface area per day for a period of 5 days and the amount of alpha interferon administered

is from 7.5 million to 12.5 million IU per m^2 of the patients body surface area administer d intraveneously or subcutaneously.

9. The method of claim 8 wherein beginning 28 days after the first day of the temozolomide administration period, the temozolomide administrations are repeated.

10. The method of claim 9 wherein the alpha interferon administered is interferon alpha 2b.

11. The method of claim 1 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

12. The method of claim 2 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

13. The method of claim 3 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

14. The method of claim 4 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

15. The method of claim 5 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

16. The method of claim 6 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than wat r for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

17. The method of claim 7 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

18. The method of claim 8 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

19. The method of claim 9 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

20. The method of claim 10 wherein the temozolomide is administered orally after the patient has fasted from food and liquids other than water for 4 hours before temozolomide administration and for 2 hours after temozolomide administration.

21. The method of claim 1 wherein the temozolomide is administered orally for a period of from 6 days to six weeks.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 96/15413

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/21 //(A61K38/21,31:53)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF CLINICAL ONCOLOGY, 13 (4). 30-03-1995. 910-913., XP000612568 BLEEHEN N M ET AL: "Cancer research campaign phase II trial of temozolomide in metastatic melanoma" see abstract ---	1-21
A	CANCER (PHILADELPHIA), 74 (3 SUPPL.). 1994. 1164-1176., XP000617951 ABRAMS J S ET AL: "New chemotherapeutic agents for breast cancer" see page 1171, column 2, paragraph 5 --- -/--	1-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 1997	26.02.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Leherte, C

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INTERNATIONAL SEARCH REPORT

Intr ional Application No
PCT/US 96/15413

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PROC ANNU MEET AM ASSOC CANCER RES;35:A1769 1994, XP000617946 CARTER CA ET AL: "Responses of human melanoma, ovarian, and colon tumor xenografts in nude mice to oral temozolomide (Meeting abstract)." see the whole document ---	1-21
A	WO 94 15651 A (STOCKHAUSEN CHEM FAB GMBH ;KLIMMEK HELMUT (DE); BREHM HELMUT (DE)) 21 July 1994 see abstract -----	1-21

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/ 15413

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-21 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/US 96/15413

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9415651	21-07-94	DE-A-	4244548	07-07-94
		AU-B-	674204	12-12-96
		AU-A-	5812894	15-08-94
		EP-A-	0676968	18-10-95
		ES-T-	2082733	01-04-96
		FI-A-	953219	29-06-95
		JP-T-	8508517	10-09-96
		LT-A,B	1560	15-07-94
		LV-B-	10782	20-08-96